Effects of DIO2 Thr92Ala SNP on Thyroid Hormonogenesis: A Narrative Review of the Literature

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Abstract:
Background: Individual genetic differences affecting thyroid hormone production may lead to treatment resistance in hypothyroid patients. Identification of these differences may lead to better treatments. *Objective*: To review the current literature examining the effect of the Thr92Ala DIO2 polymorphism on thyroid hormonogenesis. *Methods:* Literature search of scholarly databases for primary human studies investigating the impact of the DIO2 Thr92Ala polymorphism on hypothyroidism was performed. *Results and Conclusion*: The Thr92Ala SNP of the DIO2 gene has been shown to negatively impact the conversion of inactive T4 to the active T3. Hypothyroid carriers of this SNP treated solely with levothyroxine (LT4) may have suboptimal T3 levels leading to poorer outcomes.

Introduction:

Thyroid hormonogenesis is a tightly regulated and complex process crucial for normal metabolic function. Insufficient production of thyroid hormones leads to hypothyroidism which is more prevalent in Caucasians, women, and those over 60 years of age [1]. While the thyroid produces predominantly inactive T4 (thyroxine), the deiodinase enzymes are responsible for the conversion to the active T3 (triiodothyronine) via deiodination of the outer ring.

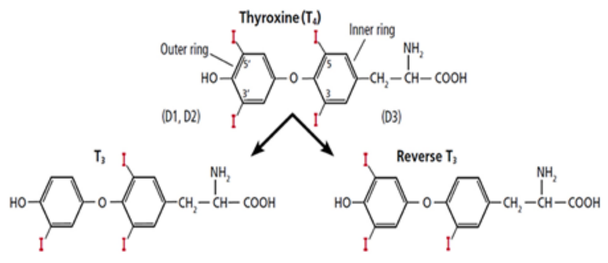

Fig. 1 - Structure of thyroxine (T4) and the deiodinative cascade to T3 and reverse T3 (rT3). Frontiers in Endocrinology., 11 December 2019 | https://doi.org/10.3389/fendo.2019.00856

The type-II iodothyronine deiodinase enzyme (D2) coded by the deiodinase-2 gene (DIO2) has a higher affinity for T4 than other deiodinase enzymes, therefore it is responsible for the majority of T3 production [2]. Insufficient enzyme cofactors and genetics may affect deiodinase activity leading to lower levels of T3. Multiple single nucleotide polymorphisms (SNPs) in the deiodinase genes have been reviewed in the literature[3] and presence of these SNPs may lead to inadequate management in patients prescribed LT4, the standard pharmacological treatment of hypothyroidism [4]. The DIO2 Thr92Ala SNP, commonly found in 12-36% of the population, is associated with a threonine (thr) to alanine (ala) substitution at the 92nd codon and this substitution has been shown to affect the activity of the enzyme [5]. This research reviews the current literature regarding the DIO2 Thr92Ala SNP and its impact on deiodinase 2 enzyme activity and peripheral conversion of T4 to T3.

Methods:

A search of the following databases; PubMed, Science Direct and Google Scholar, was performed using the following search terms: thyroid, thyroid function, hormones, serum T4, serum T3, thyroid stimulating hormone, single nucleotide polymorphism, homeostasis, HPT axis, deiodinase gene, Thr92Ala. Articles were included if they were primary studies, used human subjects, were published between 2009 – 2018, and focused solely on the DIO2 Thr92Ala polymorphism and hypothyroidism.

Results:

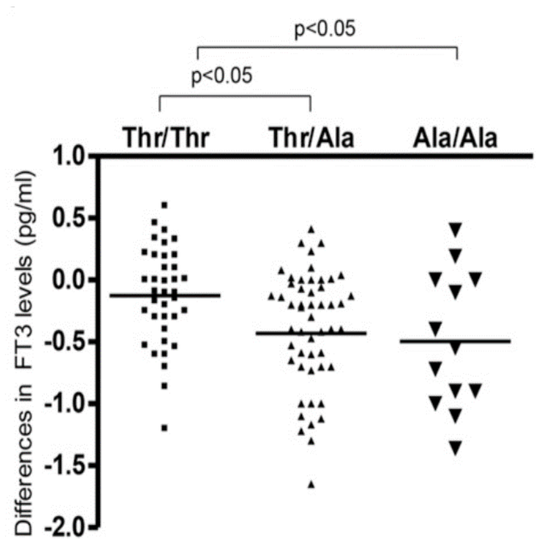

Fig. 2 – Post thyroidectomy levels of FT3 were lower in those that were homozygous (Ala/Ala) and heterozygous (Thr/Ala) for the Thr92Ala polymorphism than in those that were homozygous wild type. **Reproduced from Fig 1d**: Castagna *et al.* [6]

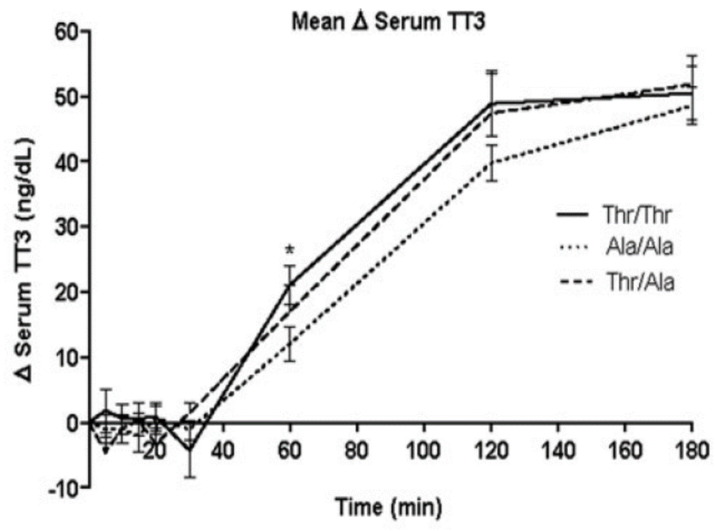

Fig. 3 – Change in serum T3 levels after TRH administration were blunted in those that were homozygous (Ala/Ala) for the Thr92Ala polymorphism compare to those that were homozygous wild type (Thr/Thr). **Reproduced from Fig 2:** Butler *et al.* [7]

TABLE 3. D2-THR92ALA POLYMORPHISM AND THYROID FUNCTION PARAMETERS IN FEMALE SUBJECTS USING LT4 AND THE GENERAL POPULATION MATCHED FOR AGE AND BODY MASS INDEX

D2-Thr92Ala	*Thr/Thr*	*Thr/Ala*	*Ala/Ala*	p-*Value*
Matched non-LT4 users				
N	733	694	154	
Age (years)	52 ± 9	52 ± 9	52 ± 10	0.913
BMI (kg/m^2)	26.7 ± 4.2	26.9 ± 4.6	27.4 ± 4.6	0.181
TSH (mIU/L)[a]	2.38 (1.69–3.41)	2.33 (1.56–3.24)	2.50 (1.77–3.21)	0.439
fT4 (pmol/L)[a]	15.6 ± 2.0	15.4 ± 2.2	15.8 ± 4.8	0.383
fT3 (pmol/L)[a]	5.1 ± 0.7	5.1 ± 0.7	5.3 ± 2.0	0.350
fT3/fT4 ratio[a]	0.33 ± 0.05	0.33 ± 0.05	0.33 ± 0.05	0.548
Subjects using LT4				
N	146	140	35	
Age (years)	52 ± 11	54 ± 12	51 ± 11	0.325
BMI (kg/m^2)	27.1 ± 4.7	26.7 ± 4.6	27.0 ± 4.1	0.802
TSH (mIU/L)[b]	2.69 (0.72–4.43)	2.71 (0.65–4.50)	2.60 (1.29–4.00)	0.997
fT4 (pmol/L)[b]	18.3 ± 3.4	18.4 ± 3.3	18.5 ± 3.2	0.975
fT3 (pmol/L)[b]	4.5 ± 0.8	4.5 ± 0.7	4.8 ± 0.5	0.399
fT3/fT4 ratio[b]	0.25 ± 0.05	0.25 ± 0.06	0.26 ± 0.03	0.706

Fig. 4 – A 2016 population study by Wouters, *et al*. found no statistical differences in thyroid parameters for female LT4 users matched for age and BMI in each of the different genotypes, but they did not analyze male LT4 users. **Reproduced and truncated from Table 3**: Wouters, *et al.*[8]

Conclusion:

This review examined the impact of the Thr92Ala SNP on DIO2 activity on T4 to T3 peripheral conversion in human subjects. This SNP results in an alanine substitution for threonine at the 92nd codon, which greatly reduces the ability of the DIO2 enzyme to properly convert T4 to T3. Ala carriers showed significant decreases in T3 levels compared to Thr carriers, with Ala homozygotes the most affected. While more studies are needed, genotyping patients for DIO2 Thr92Ala SNP may identify those ask risk for standard treatment failure leading to early use of mixed T4/T3 medications and nutritional supplementation of cofactors to support optimal peripheral conversion.

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